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PSYCHOPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL STUDIES IN SCHIZOPHRENIC PATIENTS

by
Aniko Bartfai

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ABSTRACT

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The present thesis comprises five reports from studies on two groups of strictly diagnosed schizophrenic patients (Study I, unmedicated, Study II, medicated patients), applying psychophysiological and neuropsychological methods in relation to clinical and computed brain tomography data, and CSF monoamine metabolite levels. Patients were compared to healthy subjects. Schizophrenic patients in Study I had more skin conductance (SC) responses to repeated tone stimuli and a more irregular response course than controls. Arousal was higher as indicated by faster heart rate and more SC spontaneous fluctuations, particularly in the left hand. Poor habituation to the tone stimuli was associated with few positive psychotic symptoms. All unmedicated patients showed SC responses whereas among medicated patients 33% were nonresponders. Smooth pursuit eye-tracking was impaired in both patient groups. Eye-tracking was more impaired in patients with few psychotic symptoms in both groups, and in unmedicated patients with poor SC habituation. Worse eye-tracking was associated, although weakly, to reversed occipital asymmetry (Study II), but not to monoamine metabolite levels (Study I). The patients in Study II performed worse than healthy subjects in

computerized lateralized neuropsychological tests, Finger Tapping (right but not left hand), and Trail Making, and perceived fewer Necker cube reversals. The pattern of results is in line with recent hypotheses of frontal cortical deficiency and left hemisphere overactivation/dysfunction in schizophrenia. Poor eye-tracking was associated with worse performance in Finger Tapping and Trail Making (Form A) and slower rate of Necker cube reversals, suggesting frontal cortical involvement in eye-tracking. Deviant eye-tracking and poor habituation were interpreted as signs of dysfunction in information processing, particularly in analyzing incoming stimuli in comparison with models stored in short- and long-term memory. Differences among the schizophrenic patients in relation to clinical variables suggest that psychophysiological and neuropsychological methods may be useful for subgrouping psychotic patients.

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(1) Bartfai, A., Levander, S., Edman, G., Schalling, D., and Sedvall, G. Skin conductance responses in unmedicated recently admitted schizophrenic patients. Psychophysiology, 1983. (In press.)

(2) Bartfai, A., Edman, G., Levander, S.E., Schalling, D., and Sedvall, G. Bilateral skin conductance activity, clinical symptoms, and CSF monoamine metabolite levels in unmedicated schizophrenics, differing in rate of habituation. Reports from the Department of Psychology, University of Stockholm, 1982, No. 594.

(3) Bartfai, A., Levander, S.E., and Sedvall, G. Smooth pursuit eye-movements, clinical symptoms, CSF monoamine metabolites and SC habituation in schizophrenic patients. Biological Psychiatry, 1983. (In press.)

(4) Levander, S.E., Bartfai, A., and Schalling, D. Regional cortical dysfunction in schizophrenic patients studied by computerized neuropsychological methods. Reports from the Department of Psychology, University of Stockholm, 1983, No. 595.

(5) Bartfai, A., Levander, S.E., Nybäck, H., Berggren, B.-M., and Schalling, D. Smooth pursuit eye-tracking, neuropsychological tests and computed tomography of the brain in schizophrenic patients. Reports from the Department of Psychology, University of Stockholm, 1983, No. 596.

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INTRODUCTION

The concept of schizophrenia has varied since "dementia praecox" was originally defined by Kraepelin as an enduring disorder of thought and feeling. Different features have been emphasized, such as prognosis (Kraepelin) and clinical symptoms (Bleuler, Schneider), and different forms of the disorder have been described. Recently, a distinction has been suggested by Crow (1980) between a syndrome with less cognitive impairment but with "positive" symptoms like delusions and hallucinations (Type I), and a syndrome with "negative" symptoms, e.g. loss of drive, affective flattening, and a chronic course (Type II). The new Diagnostic and Statistical Manual of the American Psychiatric Association (DSM III) proposes the following operational definition of schizophrenic disorders.

"The essential features of this group of disorders are: the presence of certain psychotic features during the active phase of the illness, characteristic symptoms involving multiple psychological processes, deterioration from a previous level of functioning, onset before age 45, and a duration of at least six months. The disturbance is not due to an Affective Disorder or Organic Mental Disorder. At some phase of the illness Schizophrenia always involves delusions, hallucinations, or certain disturbances in the form of thought."

Other common symptoms are: disturbances of affect, of sense of self, volition, relationship to the external world and psychomotor behavior. None of these symptoms is, however, specific for schizophrenia.

Some Current Models of Schizophrenia

Neuropsychological models

The neuropsychological models of schizophrenia are all based on signs of disordered information processing (attention, thinking, speech), observed in schizophrenic patients. Such disturbances were described already by Kraepelin (1919) and Bleuler (1924) as the most basic and fundamental features of schizophrenia.

One model of information processing which is relevant for interpreting disturbances in schizophrenia was suggested by Broadbent (1958), identifying three major stages of information processing: (1) sensory registration and storage, (2) perceptual analysis, and (3) response selection. In this model the capacity for sensory registration and storage is assumed to be limited, which requires fast perceptual analysis for efficient handling of information. When the analysis is slow, relevant information may be lost or distorted.

Models of information processing deviance in schizophrenia are conceptualized in terms of these stages. According to the model of

defective filter functions, the basic deficit is inadequate filtering of sensory input: external and proprioceptive. McGhie (1970) suggests that the main schizophrenic deficit is the inability to screen out irrelevant information while Yates (1966) puts the emphasis on the low speed of information processing. Lehmann (1966) suggested that the defective filtering might be an underlying trait since there are also in healthy normals wide individual variations in the ability to cope with excessive amount of information.

Venables (1973) postulated a decreased capacity for "gating out" irrelevant stimuli in schizophrenics as a result of hippocampal dysfunction. This inability is reflected in certain aspects of electrodermal responding, e.g. fast recovery.

A different line of neuropsychological research focuses on localizing and studying specific dysfunctions in schizophrenic information processing. There is a growing evidence reviewed by Walker and McGuire (1982) for left-hemispheric overactivation in schizophrenia and a consequent disturbance of information processing.

Venables (1982) considered left-hemispheric overactivation as a secondary phenomenon. According to this hypothesis there is, at some stage of an individuals development, a primary right-hemisphere inadequacy which leads to a transfer of activities to the left hemisphere. This transfer of tasks results in impaired performance via three mechanisms: (1) Tasks that are normally excecuted by the global type of right-hemispheric strategies have to be solved by the serial type strategies available to the left hemisphere. (2) The overcrowding of tasks in the left hemisphere results in interference and competition for processing capacity between tasks. (3) A consequent increase in left hemisphere arousal beyond the optimal level leads to impaired performance according to the inverted U relation between arousal and performance.

Biochemical models

Among the different biochemical models of schizophrenia the dopamine hypothesis has been most fruitful in understanding possible biochemical disturbances in schizophrenia (Haracz, 1982). The dopamine hypothesis was originally based on indirect pharmacological evidence: the finding that antipsychotic drugs block central dopamine receptors (Carlsson & Lindqvist, 1963; Creese, Burt & Snyder, 1976). The implication of a dopaminergic hyperactivity in schizophrenia has not been verified in studies on schizophrenic patients (Carlsson, 1978). No aberrations have been found in level of the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid of schizophrenics (Sedvall, Fyrö, Nybäck, Wiesel & Wode-Helgodt, 1974). However, the variance of HVA levels was larger in schizophrenics than in controls (Sedvall & Wode-Helgodt, 1980), indicating that there are subgroups of patients with deviant dopaminergic activity. Further, evidence of dopaminergic hyperactivity comes from recent findings in postmortem brain samples showing increased dopamine receptor density in schizophrenic patients, who had been free of neuroleptics (Owen, Cross, Crow, Longden, Poulter & Riley, 1978).

Psychophysiology

Assumptions, Models and Measures

Psychophysiology deals with the measurement of changes in physiological activity attendant upon "psychological" changes and conditions. The emphasis is generally on noninvasive techniques. Psychophysiology comprises e.g. monitoring of electrodermal, cardiovascular, respiratory, vasomotor, skeleto-muscular, ocular, and electroencephalographic (both rhytmic and evoked responses) measures.

Psychophysiological research within the field of psychiatry started in the beginning of this century. Jung (1907) used measures of electrodermal activity in his earliest work with the free association method. Since then a wide range of psychophysiological methods have been applied in research concerned with human information processing capabilities and with diagnosis and prognosis of psychiatric disturbances such as schizophrenia, manic-depressive illness, and psychopathy. In the following the most commonly used parameters will be described.

Skin conductance and heart rate measures

Electrodermal (skin conductance, SC) measures are widely used in psychophysiological research since the discovery of the "psychogalvanic reflex" in 1888 by Féré. The present applications are based on the observation that the ability of the skin to conduct a weak electric current is related to CNS-controlled sweat gland activity.

Tonic aspects of the SC measures such as the level of SC (SCL), and the number of spontaneous response-like fluctuations (SF) in the absence of external stimuli are assumedly reflecting aspects of arousal (Katkin, 1975), and fantasy and imagery (Schalling, 1978).

Phasic changes (max 15 sec) are regarded as responses (SCR) to external or internal stimuli. The SC component of an *orienting response* (OR) occurs in the presence of a novel or changed stimulus. The OR is a general phenomenon, i.e. not specific to the nature of the eliciting stimulus. It demonstrates habituation, i.e. the various components of the OR decrease in amplitude or in likelihood of occurrence upon successive presentations of the same stimulus.

Defense responses (DR) elicited by intense or noxious stimulation occur relatively faster than the OR and do not demonstrate habituation, unlike *startle responses*, also elicited by relatively intense, unexpected, but not necessarily noxious stimuli.

The following aspects of the SC response (SCR) are often evaluated: latency, rise-time, amplitude, and recovery. Among these the *recovery* of the response deserves particular emphasis because of the theoretical aspects of this measure. From a series of studies, Edelberg (1970, 1972) concluded that the recovery of the SCR varies with different situational demands and stimulus properties. Fast recovery reflects mobilization for goal directed behavior, while slow recovery is associated with aversive stimuli or situations. The central pro-

cess interpretation of the recovery measure has, however, been questioned by some workers (Bundy & Fitzgerald, 1975). There is still disagreement among researchers on this issue.

The most important SC response parameter in the present context is *habituation*. The habituation, i.e. the reduction and eventual cessation of responses to repeated identical stimuli is essential for the elimination of unimportant input from the environment, thereby maintaining an optimal level of arousal and attention. Habituation is a central phenomenon and an active process of response inhibition. According to Sokolov (1963) repeated presentation of a stimulus leads to the formation of a "neuronal model" of the stimulus and its salient attributes in the cortex. At each stimulus presentation the correspondence between the input and the model determines the strength of an inhibitory signal which is modulating the activating effect of incoming signals at the level of the reticular system.

According to Öhman (1979) the autonomic concomitants of an OR reflect a call to initiate central processing of a stimulus. It is assumed that the stimulus to be processed is selected by preattentive mechanisms. These mechanisms interact with memory stores containing stimulus representations. When the preattentive mechanism fails to identify the stimulus because there is no matching representation in the memory stores, an OR is elicited. Habituation of the OR would thus depend both on the preattentive mechanisms and on the capacity to form new memory images.

Habituation of the SCR is operationally defined in terms of a response decrement following administration of repeated stimuli. The measures of habituation have varied across studies and the measures used probably reflect different aspects of habituation (O'Gorman, 1977). The most commonly used measure is the number of trials to habituation, i.e. the number of stimulus presentations until three consecutive non-responses. This measure reflects how fast the subjects arrive at the habituation criterion, while other measures take the changes in response amplitudes into account, and thus describe the habituation process. One such measure is the number of amplitude inversions, which is based on the assumption that each SCR larger than the preceeding SCR represents a disruption in the habituation process (Levander, Schalling, Lidberg & Lidberg, 1979).

Heart rate (HR) changes reflect the action of complex homeostatic mechanisms subserving the purpose of maintaining an optimal blood supply to all organs, but have been shown to reflect also psychological processes (for a discussion see Levander, 1979). Thus, an increase in HR level may be effected both by physical exercise and for instance the subject's intention to involve in physical exercise. The HR response to stimuli typically comprises three components within approximately 10 secs after stimulus onset. Since the multicomponent HR response allows discrimination between orienting, defense and startle responses, in contrast to the one-component SCR, it has received special attention in psychological research (Graham & Clifton, 1966).

Smooth pursuit eye-movement (SPEM) measures

Pursuit eye-movements are recorded while a pendulum or another target with similar motion is moving in front of the subject. Diefendorf and Dodge (1908) found disrupted pendulum tracking behavior in psychiatric patients, particularly schizophrenics. The authors related this finding to clinically observed attentional disturbances in these patients. However, the method was not used until 1973, when Holzman and collaborators found markedly increased incidence of smooth pursuit eye-movement impairment in schizophrenic patients (Holzman, Proctor & Hughes, 1973). SPEM is assumed to reflect both attentional (the capacity to voluntarily focus attention on a task) and preattentional (automatic complex stimulus-analyzing) mechanisms. Furthermore, it requires intact function of oculomotor mechanisms.

Psychophysiological Research in Schizophrenia

The earliest studies attempted mainly to identify reliable differences between schizophrenics and nonpsychotic subjects in tonic and phasic ANS (Autonomic Nervous System) activity (for a review see Lang & Buss, 1965). In later studies psychophysiological measures have also been used as indicators of aberrant internal states and functions, applying theoretical constructs such as "arousal" and "attention". The use of psychophysiological parameters is of particular interest in schizophrenia research, since in many experimental paradigms these measures are free from bias due to inattention and low motivation. The current focus of interest is on integration of ANS and CNS measures into meaningful patterns (Venables, 1975).

Skin conductance and heart rate

Research on the SC responding pattern in schizophrenia has been stimulated by the work of Bagshaw and her coworkers (Bagshaw, Kimble & Pribram, 1965) on monkeys. The experiments indicated that amygdalectomized monkeys showed a hyporesponsive while hippocampectomized animals had a hyperresponsive electrodermal pattern. The results focused the interest on the inhibitory role and control functions of the limbic system in stimulus processing. Gruzelier and Venables (1972, 1973) reported that 50% of the schizophrenic patients were nonresponders, i.e. did not exhibit SCR, while the remaining 50% did not habituate to a series of tones. The results were interpreted within the conceptual framework of input regulation by the limbic system. Such a sharp dichotomy as reported by Gruzelier and Venables has not been replicated in later studies but bimodality or skewness in the distribution of SC responses has been found in a majority of studies.

According to a review by Öhman (1981) the reported proportion of nonresponders in schizophrenic groups varies (0 and 68%) with a median close to 40%. The frequency of nonresponding appears to vary with stimulus intensity (Bernstein, 1970; Bernstein, Schneider, Juni, Pope & Starkey, 1980) and stimulus significance (Gruzelier & Hammond, 1978). However, neither the differences in stimulus intensities across studies, nor the different methods of measurement used, can fully account

for the differences in proportion of nonresponders (Öhman, 1981).

An increased frequency of nonhabituators in schizophrenic groups has been found in a series of studies (Gruzelier & Venables, 1972; Rubens & Lapidus, 1978; Frith, Stevens, Johnstone & Crow, 1979). However, some studies report faster habituation among schizophrenics than among controls (Bernstein, 1970; Bernstein et al., 1980). A subgroup of schizophrenic responders has been identified as "fast habituators" (Patterson, 1976; Patterson & Venables, 1978), exhibiting SC responses only to the first and the second stimulus. Considerable effort has been spent to reconcile these differences among studies since the issue of habituation is of particular importance in view of the disordered information processing in schizophrenia (Bernstein, Frith, Gruzelier, Patterson, Straube, Venables & Zahn, 1982).

The *recovery time* of the SC response has received great interest since it has been shown to discriminate fairly consistently between schizophrenics and controls, with the patient group having faster recovery (Ax & Bramford, 1970). Similar findings were obtained by Gruzelier and Venables (1972), Rubens and Lapidus (1978) and Zahn, Carpenter and McClashan (1981). The recovery of SCR was found to be the only psychophysiological measure predicting psychiatric breakdown in a group of children at high-risk for schizophrenia (Mednick, 1970). Venables (1975) hypothesized that fast recovery is an index of exceptional "openness" to environmental stimulation, leading to an overload of sensory input in schizophrenia. However, findings of fast recovery in schizophrenic groups are not quite consistent. Gruzelier, Eves, Conolly and Hirsch (1981) and Patterson and Venables (1978) did not obtain differences in recovery between patients and controls.

Lateral measures in SC measures have also been studied. According to prevailing hypotheses the excitatory control of SC is ipsilateral or bilateral, while the inhibitory control is contralateral (Smith & Ketterer, 1982). Larger right than left hand SC responses in schizophrenic patients have been reported in some studies (Gruzelier & Venables, 1974; Patterson & Venables, 1978) but not in others (Gruzelier et al., 1981). No consistent differences have been obtained in tonic measures between left and right hands. Öhman (1981) concluded tentatively that the larger right hand responses probably reflect loss of inhibitory control from the left hemisphere.

Studies of *heart rate* in schizophrenic patients generally indicate higher tonic levels as compared to controls (Spohn, Lacoursiere, Thompson & Coyne, 1977; Zahn, Rosenthal & Lawlor, 1968; Tarrier, Cooke & Lader, 1978).

Smooth pursuit eye-movements

In a series of studies impairment in smooth pursuit eye-movements in schizophrenic groups has been consistently demonstrated (Holzman et al., 1973; Holzman, Kringlen, Levy & Haberman, 1980). The pursuit impairment is not a result of a deficit of peripheral eye-control mechanisms (Iacono, Tuason & Johnson, 1981; Latham, Holzman, Manschreck & Tole, 1981). The quality of smooth pursuit eye-movements can be improved to a certain degree by manipulations of voluntary attention (Shagass, Roemer & Amadeo, 1976; Holzman, Proc-

tor, Levy, Yasillo, Meltzer & Hunt, 1974; Pivik, 1979; Levin, Lipton & Holzman, 1981b; Brezinova & Kendell, 1977; Acker & Toone, 1978).

There is an overlap in eye-tracking deficiency between schizophrenic patients and healthy controls. Because of the high genetic loading (Holzman et al., 1974; Holzman, Kringlen, Levy, Proctor & Haberman, 1978; Holzman et al., 1980) and because the impairment is present also during remission (Iacono et al., 1981) it is likely that impaired SPEM represents a biological vulnerability indicator rather than a symptom of the disease.

Neuropsychological Research in Schizophrenia

The presence of perceptual and cognitive deficits among schizophrenic patients has been repeatedly demonstrated both by use of conventional neuropsychological tests such as those included in the Wechsler Adult Intelligence Scale (WAIS) and the Halstead-Reitan battery (Heaton, Baade & Johnson, 1978; Flor-Henry & Yeudall, 1979), and by the use of more specific tasks (Payne, 1972).

In general, conventional neuropsychological tests do not distinguish between schizophrenic and organic conditions. Although schizophrenic patients generally display an "organic" type of deficit, the interpretation of such findings is difficult due to the attentional and motivational disturbances characteristic of schizophrenia. By the use of specific neuropsychological tests, it has been shown that schizophrenic patients display characteristic disturbances in e.g. proprioception, abstract thinking and perception (Venables, 1978). In recent years the possible lateralization of cognitive dysfunction in schizophrenia has received an increased interest. Conventional neuropsychological tests do not appear to be particularly useful in such research, whereas more experimental approaches have yielded highly interesting results suggesting impairment of lateralized cognitive functions (Gur, 1979; Walker & McGuire, 1982).

Although disturbances in groups of schizophrenics have been demonstrated by a wide range of psychophysiological and neuropsychological methods, there are still many points of disagreement among different studies. This is not surprising taking into account the lack of diagnostic rigour and control for medication effects in many studies, and the clinical heterogeneity among the "schizophrenics".

AIMS OF THE PRESENT WORK

The purpose of the present work was to contribute to the analysis of disturbed cognition in schizophrenia by the application of psychophysiological and neuropsychological methods in schizophrenic patients, diagnosed according to explicit research criteria.

The specific aims were: (1) to explore the usefulness of the methods in relation to clinical data, and biochemical and brain

morphological measures, (2) to analyze findings in terms of current models of regional and lateralized cortical dysfunction in schizophrenic patients, (3) to interpret findings within models of information processing, preattentive mechanisms and arousal.

METHOD

General Design

The present work comprises two studies. In Study I (Reports 1, 2 and 3) skin conductance, heart rate and smooth pursuit eye-movements were recorded in a group of unmedicated recently admitted schizophrenic patients, in a small group of paranoid psychotic patients (only skin conductance and heart rate measures), and their age- and sex matched controls. In Study II (Reports 4 and 5) skin conductance, heart rate, smooth pursuit eye-movements were recorded and three computerized neuropsychological tasks, Finger Tapping/Alternation, Trail Making and a figure reversal task, the Necker cube, were administered in a group of medicated schizophrenic patients. The results in the neuropsychological tests were compared with those in a group of healthy male subjects.

The studies were approved by the Ethics Committee of the Karolinska Hospital.

Subjects

Patients (Study I). Patients were recruited among drugfree patients admitted to an open research ward at the psychiatric clinic of the Karolinska Hospital. The clinic which serves a catchment area of approximately 250.000 inhabitants has the only 24 hour emergency psychiatric service in its district. The emergency service is the major source of referrals to the research ward, which admits patients with psychotic symptoms of sufficient severity to merit hospitalization but not so out of control that treatment in an open ward is considered impossible. The initial selection of patients was thus made on clinical grounds and no patient was admitted for research purposes only. Selection of patients for the studies was made by the psychiatrist in charge of the research ward. The preliminary inclusion criterion was presence of at least one psychotic symptom (hallucinations, thought disorders or delusions). Exclusion criteria were drug or alcohol abuse, and a history of affective disorder or organic cerebral disease. The upper age limit was 45 years. During a period of 24 months all 40 patients meeting these preliminary criteria were asked to participate. Three patients refused. Thirtyseven patients consented and participated in the procedure described below. Of these, nine were excluded before data evaluation, because they were found not to fulfill all criteria.

A final diagnostic assessment was performed for the remaining 28 patients on the basis of case records and available clinical ratings, by two psychiatrists, Göran Sedvall and Sten Levander. They independently classified the patients according to the Research Diagnostic

Criteria (RDC) described by Spitzer, Endicott and Robins (1978). The diagnosis was identical in 25 of 28 cases. Two patients were classified as schizophrenic by one and probably schizophrenic by the other psychiatrist. One patient was classified as probable schizophrenic by one and as having an unspecified psychotic disturbance by the other. Patients were classified in the following categories: a) Schizophrenics, (n = 13); b) Schizophrenics (disagreement as to schizophrenic or probable schizophrenic between judges), (n = 2); c) Unspecified Psychotic Disorder, Paranoid State, (n = 5); d) Other psychotic disturbances, (n = 3); e) Other categories, (n = 5). In the following, patients in categories a and b are treated together (n = 15).

Five patients were classified as having Unspecified Psychotic Disorder, Paranoid state according to the RDC. Of the three patients classified as having other psychotic disturbances, two were diagnosed as having borderline personality disorder and one patient had mutism. Clinically these patients had schizophrenic features, but because of the positive symptoms required by the RDC, they were classified as non-schizophrenic. The remaining patients were classified as: non-psychotic disorder (2), epilepsy (1), affective-psychotic disorder (1), drug addiction (1).

Of the 15 schizophrenic patients two did not have complete skin conductance recordings. One of these patients refused continued participation after the first tone and the other lost the SC electrodes while moving his hands. These two patients were excluded. One of the remaining schizophrenic patients did not have satisfactory eye-movement recordings due to technical difficulties. Thus, 13 schizophrenic patients were included in Report 1 and 2, and 12 in Report 3.

The schizophrenic patients were further classified according to RDC subtype and course of the illness. The two judges agreed in 12 of 13 patients for subtype and in 11 of 13 for course. Five patients were classified as "undifferentiated", five as "paranoid" and three as "hebephrenic" schizophrenics. The course classification was "subacute" for one patient, "subchronic" for six and "chronic" for six. None of the patients was classified as "residual", i.e. having only negative symptoms. Thus, all 13 patients showed positive schizophrenic symptoms at the time of the psychophysiological testing. Twelve had delusions and ten hallucinations. Those who did not hallucinate had multiple bizarre delusions and cognitive disturbances.

No patient was taking antipsychotic or other psychoactive drugs during the period of testing. Six patients had been on antipsychotic medication before; the drugfree interval ranged between 3 weeks and 4 years (median 7 weeks). Background data for the schizophrenic group are given in Table 1. Mean age was 28.9 (range 19-42). Educational and professional level varied widely.

At a follow-up study carried out two to four years later data were available for 12 of the 13 patients. (One patient had moved abroad). Six of the patients were institutionalized permanently or had had several severe recurrent schizophrenic episodes. One patient had committed suicide. Five patients were living in the community. Most of them were on medication and received some degree of supportive treatment.

Table 1. Demographic and clinical data for schizophrenic (n = 13) and paranoid psychotic (n = 5) patients in Study I.

Variable	Schizophrenics	Paranoid psychotics
Age (mean)	28.9 yrs	37.0 yrs
Age (range)	19-44 yrs	29-44 yrs
Sex (male; female)	8; 5	3; 2
Number of patients with previous psychotic episodes	5	0
Age at the first psychotic episode (mean)	24.8 yrs	37.0 yrs
Time since beginning of first psychotic episode (median)	2.0 yrs	0.5 yrs
Number of patients with previous antipsychotic medication	6	0

Results for the five patients diagnosed as paranoid psychotics (3 males, 2 females, mean age 37 years, range 29-44) were also analyzed in Reports 1 and 2. The homogeneity of the group in many relevant aspects justified analysis of the data in spite of the low number of patients. For all patients the present psychotic episode was their first one, none of them had received antipsychotic medication before, and the duration of the present episode was less than one year. They were well educated with qualified professions and had a good social background.

Controls (Study I). Thirtyeight healthy volunteers (22 men, 16 women, mean age 29.1, range 19-45) were recruited from hospital staff, medical studients and fire men. Exclusion criteria were a history of severe head injury, somatic disease or psychosis and exposure to antipsychotic drugs. Subjects were paid for participation. Since age and sex may influence the psychophysiological measures, a pair-matching was performed, selecting one control group with a mean age of 28.6 years for the schizophrenic patients (n = 13) and one control group with a mean age of 36.6 years for paranoid patients (n = 5), excluding controls with a family history of psychiatric morbidity. However, one such control had to be included for the paranoid patients.

Patients (Study II). A total of 26 inpatients in the research ward were diagnosed as schizophrenic according to RDC criteria during 1 1/2 year after the completion of Study I. Of these patients seven were still hospitalized on the research ward when Study II was initiated, while the remaining patients were discharged from the hospital. All 26 patients were approached and invited to participate in Study II. Discharged patients were offered payment to participate on the same basis as is customary for healthy subjects. One of the still hospitalized patients refused to take part. Three of the discharged patients could not be reached. Two were currently hospitalized in a mental hospital and were too ill to be tested.

Table 2. Demographic and clinical data for schizophrenic patients in Study II (n = 18).

Variable	Patients
Age (mean)	29.7 yrs
Age (range	23-42 yrs
Sex (male; female)	11; 7
Number of patients with previous psychotic episodes	10
Number of patients with previous antipsychotic medication	9
Number of patients with poor premorbid adjustment	8
Number of patients with family history of psychiatric morbidity	10
Number of patients according to:	
RDC subtype	
hebephrenic	9
paranoid	4
undifferentiated	3
catatonic	1
residual	1
RDC course	
acute	2
subacute	5
subchronic	5
chronic	6

Two discharged patients refused participation. They were recovered, well adjusted and did not want to be reminded of their hospitalization. Thus, 18 subjects participated in Study II, twelve outpatients and six inpatients. The group consisted of 11 men and 7 women (mean age 29.7 years, age-range 23-42 years). Background data for the group are given in Table 2. Sixteen patients were on medication at the time of the investigation.

Poor premorbid adjustment was defined as "pronounced difficulties in peer relations" in combination with neurotic, psychosomatic or social problems (mobbing) or as psychiatric problems requiring contact with child psychiatric institutions, during the period from 12 to 18 years of age until onset of the psychotic disturbance. Family history of psychiatric morbidity was assessed as occurrance of psychiatric hospitalization among siblings, parents and siblings of parents.

Comparison group (Study II). Eightyfour male subjects (mean age 23 years, range 22-24) randomly selected from Solna, a suburban town within the catchment area of the hospital, served as a comparison group for the schizophrenic patients in Study II (Report 4). Selection procedures are described in a report from a previous study on these subjects (Olweus, Mattsson, Schalling & Löw, 1980).

Procedure

The procedure for Study I is described in detail in Reports 1 and 3, for Study II in Report 5. Briefly, bilateral skin conductance, heart rate and respiration rate were recorded during tone stimulation (Study I, 21 tones, Study II, 15 tones) and rest (5 min) before and after the tone series. Tone stimuli were identical for both studies (1000 Hz, 85 dB, 1 sec, 0.25 msec rise time). Smooth pursuit eye-movements were recorded for two stimulus velocities (sinusoidal and triangular), (Study I, 8 trials; Study II, 13 trials). In Study II three computerized neuropsychological tests were administered: the Finger Tapping test, the Trail Making test and a figure reversal task, the Necker cube.

Registration and Quantification of Psychophysiological Measures

The psychophysiological laboratory equipment used for the registration of skin conductance and heart rate measures in the present work has been used in a series of previous studies and is described in detail in Levander (1979) and in Reports 1 and 2.

Bipolar skin conductance (SC) recordings were obtained from the thenar and hypothenar eminences of the left and right hand. The folowing SC parameters were evaluated: SC level, SC responses to tones, number of SC spontaneous fluctuations, two measures of habituation of SC responses, and recovery time of SC responses.

Heart rate (HR) was recorded as consecutive interbeat intervals using a photopletysmographic transducer attached to one cheek. HR level and responses to tones were evaluated.

Respiration rate was recorded with a strain-gage transducer. Data were used to correct for artefacts due to irregular respiration in skin conductance and heart rate registrations.

The stimulus parameters and electrooculographic (EOG) recording techniques for *smooth pursuit eye-movements (SPEM)* followed methods described by Holzman et al. (1974) and Shagass, Amadeo and Overton (1974). Horizontal eye-movements were recorded by electrodes applied to the outer canthi of both eyes and a ground electrode, attached to the middle of the forehead. The method is described in Reports 3 and 5.

The EOG recordings were rated visually for deviance from the stimulus pattern and for irregularity on a five point scale, similar to the one used by Shagass et al. (1974). The ratings were made blindly with regard to group by two independent raters. The interrater reliability was 0.86 in Study I and 0.79 in Study II. Disagreements in ratings were resolved by consensus.

Neuropsychological Tests

Three computerized tests were implemented on an Apple II microcomputer with a Video 100 video display unit (VDU). A detailed description is given in Report 4, Appendix.

Finger Tapping and Alternation. The computerized version comprised four subtests (1) right, and (2) left index finger tapping, (3) right and (4) left index-middle finger alternation. The score was the number of tappings/alternations for each subtest.

Trail Making test. The computerized Trail Making Test was based on the paper and pencil version of this test included in the Halstead-Reitan neuropsychological battery (Lezak, 1976). The computerized version comprised three parts: (1) a training session, (2) a session comprising two "Form A" tasks (digits from 1 to 9) and one "Form B" task (digits and letters from 1-A to 9-J) for the preferred hand, and (3) an identical session for the non-preferred hand. Digits and letters were presented on the VDU. The score was the mean of the individual hit times for each task.

Necker cube. A perspective drawing of a cube, the Necker cube, was administered in a computerized version. Subjects were seated 60 cm in front of the VDU. The Necker cube (15 x 15) was presented for 90 sec on the VDU. Scores were the number of perceived alternations in 90 sec, the mean time (sec) between alternations (intervals) and the time to the first alternation (latency).

Biochemical Measures

Cerebrospinal fluid (CSF) samples were available for patients and matched controls in Study I. The CSF samples were obtained and treated as described by Sedvall and Wode-Helgodt (1980). The determination of the monoamine metabolites, homovanillic-acid (HVA), 5-hydroxy-indole-acetic-acid (5-HIAA) and 3-methoxy-4-hydroxy-phenylethylene glycol (MHPG) was carried out according to Swahn, Sandgärde, Wiesel and Sedvall (1976).

Computed Brain Tomography (CT) Measures

CT scans were performed in the Department of Neuroradiology, Karolinska Hospital. Four morphological parameters were estimated: (1) the size of the lateral ventricles, (2) the size of the third ventricle, (3) widening of hemispheric sulci, (4) incidence of reversed asymmetry of the frontal and occipital lobes. Details are given in Report 5.

Clinical Data

Clinical data for the patients in the two studies were obtained regarding previous hospitalization, previous medication and premorbid

adjustment. Data were based on extensive information available in case records for Study I. In Study II the data were in addition based on a detailed, semistructured interview conducted by the staff psychiatrist with the patient and when possible (66% of the cases) with a parent.

The use of the CPRS rating scale. Ratings of clinical symptoms were made according to the Comprehensive Psychopathological Rating Scale (Åsberg, Montgomery, Perris, Schalling & Sedvall, 1978) which consists of 65 items (40 reported and 25 observed) covering a wide range of psychiatric symptoms, and a global rating of illness. CPRS is designed as a pool of items from which shorter scales can be selected. For Reports 2 and 3 five subscales were constructed. In Study II patients were rated on the day of the psychophysiological testing on 16 items found to be most sensitive to change after treatment of schizophrenic patients (Härnryd, Bjerkenstedt, Björk, Gullberg, Oxenstierna, Sedvall, Wiesel, Wik & Åberg-Wistedt, 1983).

RESULTS AND COMMENTS

Skin Conductance and Heart Rate Measures in Schizophrenic Patients

Tonic autonomic measures

The results for the tonic psychophysiological measures in Study I (Report 2) indicate higher arousal in the schizophrenic group as compared to controls both during rest and tone stimulation. HR level and the number of SC spontaneous fluctuations were significantly higher and the same trend, although nonsignificant, was observed for SC levels. In addition there were significantly more SC spontaneous fluctuations on the left hand for the schizophrenic group as compared to the right hand (Fig. 1) which was interpreted in view of hypotheses of ipsilateral excitatory control of SC was interpreted as additional evidence for left hemispheric overactivation in schizophrenic patients. Analyses of SC measures in Study II (manuscript in preparation) indicate that these medicated patients displayed lower arousal, estimated by SC levels, than the unmedicated patients in Study I. Differences between nonresponders, habituators and nonhabituators within the group were significant ($p < .05$ for both hands), nonresponders having the lowest and nonhabituators the highest SC level.

The issue of SC nonresponding

One of the major findings in Study I is the absence of nonresponders. This result is discussed in Report 1 in terms of stimulus characteristics (85 dB, 0.25 msec rise time), medication effects (all patients were unmedicated, 7 patients had never taken antipsychotic drugs), and patient characteristics (all patients were in an acute phase of their illness). The effects of stimulus characteristics (rather high intensity, fast rise time) were particularly stressed. In Study II, however, 33% of the patients were nonresponders (Table 3), a figure close to the median percentage of nonresponders

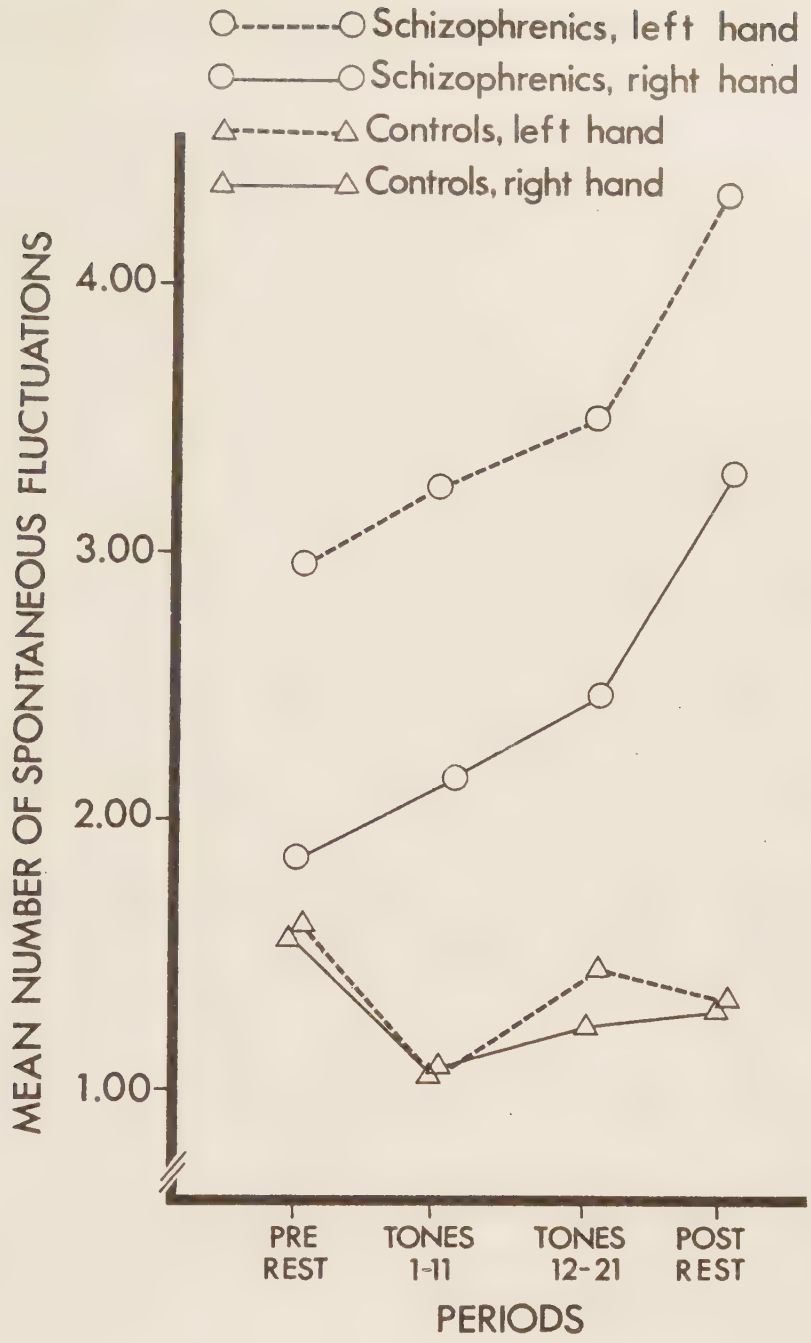

Fig. 1. Frequency of spontaneous fluctuations in left and right hand SC recordings during prestimulation rest, repeated identical tones and post-rest periods in schizophrenic patients and controls in Study I.

(40%) in a large number of studies reviewed recently by Öhman (1981). Stimulus characteristics(intensity, rise time) were identical in the two studies. However, the patients in Study II differed from the patients in Study I in two important aspects: most of them were medicated, and neither in- nor outpatients were in an acute or exacerbating phase of the illness. Nonresponders were equally distributed among in- and outpatients (X^2 = 0.28, df = 1, ns) and did not differ from re-

sponders in the global rating of severity of illness according to the CPRS-scale.

Table 3. Distribution of schizophrenic patients according to rate of SCR habituation to 11 tone stimuli. Habituation was estimated by the criterion of three consecutive nonresponses (H-crit).

	Nonresponders		Habituators		Nonhabituators	
	left hand	right hand	left hand	right hand	left hand	right hand
Study I (unmedicated patients) n = 13	0	0	6	7	7	6
Study II (medicated patients) n = 18	6	6	7	7	5	5

Reports on the effects of medication on SC nonresponding are inconclusive. Most studies (reviewed by Öhman, 1981) conclude that antipsychotic medication does not influence phasic SC characteristics such as SC responses, as opposed to tonic aspects (SC level). Nonresponding has also been found in studies on unmedicated patients (Frith et al., 1979; Straube, 1979; Zahn et al., 1981). However, a blocking effect of antipsychotic drugs on the peripheral (cholinergic) receptors mediating SC activity was demonstrated by Koss and Davison (1976). In Study I previous medication obviously did not lead to nonresponding, and in Study II responders and nonresponders were equally distributed among previously medicated and unmedicated patients (Fisher's exact test p = 1.00), thus long term antipsychotic medication does not seem to influence SC responding - nonresponding. Effects of concurrent medication cannot be excluded on the basis of data in Study II since the effects of the phase of illness and of medication are confounded. Further systematic studies are needed to separate these two factors to examine differential effects of antipsychotic drugs with regard to type and dosage.

SC responsivity

In Report 2 five different estimates of SC responsivity were analyzed. All measures except the conventional habituation criterion of three consecutive non-responses (H-crit) indicated higher responsivity in schizophrenics. The findings indicate a relative insensitivity of this conventional criterion in groups, like ours, where there is a marked tendency for dishabituation (Report 2, Table 3) and irregular response course. In such groups the habituation process may be better described by other habituation estimates such as the inversion measure (H-inv) or by evaluation of response rates after the conventional criterion is reached.

The recovery time of the SC response did not differ in the unmedicated schizophrenic group as compared to controls (Study I, Report 2), an unusual but not unique finding (Gruzelier et al., 1981; Patterson & Venabler, 1978). Aversive stimulus properties (high intensity, fast rise time) might have caused prolonged recovery times in the present study. The differences in results between the present work and earlier studies may in part reflect statistical bias due to uncorrected skewness and excessive weight of responses late in the response sequence in previous reports.

Differences between SC nonhabituators and habituators

The nonhabituator status has been shown to be fairly stable in two studies (Zahn et al., 1981; Frith et al., 1979). The classification was not related to clinical changes following treatment. Thus, poor habituation appears to have trait character. In Report 2 habituating and nonhabituating patients were compared with respect to psychophysiological, clinical and biochemical variables. Nonhabituators had significantly more SC spontaneous fluctuations (Report 2, Fig. 2), showed significantly less positive symptoms and had lower rated global severity of illness (Report 2, Table 4). Nonhabituating was interpreted as an indicator of vulnerability in a subgroup of patients with negative symptoms. Nonhabituators and habituators did not differ in the CSF levels of monoamine metabolites: HVA, 5-HIAA and MHPG.

In Study II (medicated patients) nonhabituators did not differ from the remaining patients in global rating of illness but tended to have higher ratings on the item "Inability to feel" (Kruskal-Wallis, corrected for ties, $X^2 = 5.73$, $df = 2$, $p < .10$).

Skin Conductance and Heart Rate Measures in Paranoid Psychotic Patients

The group of paranoid psychotic patients (Reports 1 and 2) was small ($n = 5$) but homogenous in terms of symptomatology, clinical background and social adjustment. The paranoid group did not differ significantly from their matched controls but showed similar trends as for the schizophrenic patients in CS and HR levels except for a steadily decreasing trend during the session for SC spontaneous fluctuations (Report 2). The most noteworthy finding was the stable habituation in this group as compared to the matched controls (Fisher's exact test, $p = 0.05$). According to Sokolov's model (1963) the superstable pattern of habituation would indicate a tendency to rapidly form rigid models of incoming stimuli.

Smooth Pursuit Eye-movements (SPEM) in Schizophrenic Patients

Both studies confirmed previous findings of pursuit eye-tracking impairment in schizophrenic patients. In Study I (Report 3) unmedicated schizophrenic patients had more impairment than matched healthy controls (Fig. 2). In Study II (Report 5) the percentage of medicated

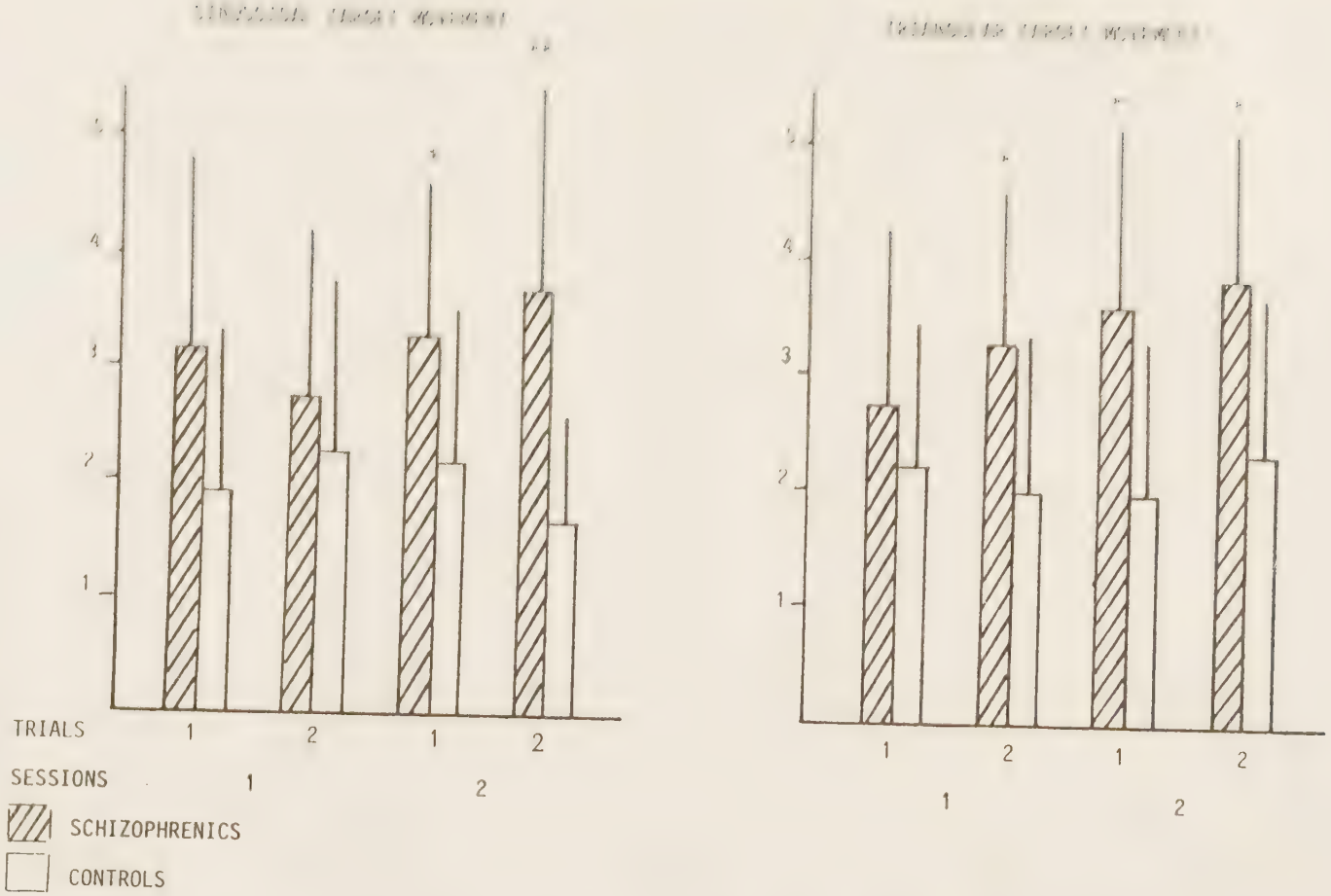

Fig. 2. Means and standard deviations of SPEM measures for the two types of target movements (sinusoidal and triangular) for schizophrenic patients and controls in Study I. (+ $p < .10$, * $p < .05$, ** $p < .01$).

patients with some degree of impairment was high (83% for sinusoidal and 92% for triangular stimulus pattern) as reported in some previous studies (Holzman et al., 1974).

SPEM and clinical ratings

In Study I patients with more impaired eye-tracking had less psychotic symptoms (Fig. 3). In Study II the eye-movement impairment of medicated patients was not related to the global rating of illness and was negatively related to ratings of some CPRS items: "feeling controlled", "ideas of persecution" and "inner tension" (anxiety) (Report 5, Table 2). Thus patients with less florid symptomatology (and possibly relatively more negative symptoms) had more marked eye-movement impairment. Classifications according to subtype and course of the illness were not related to eye-movement impairment.

The results of both studies indicate that pursuit eye-movement impairment is more pronounced in subgroups of schizophrenics with relatively few positive symptoms; the deviance is independent of the phase of illness (acute or remitted) and of global ratings of the severity of illness. Earlier studies (Holzman et al., 1974) have found increased incidence of pursuit eye-movement deviance in relatives of schizophrenic patients. Thus, the impairment appears to reflect to a large extent some underlying disturbance with trait character.

SPEM and indices of SC responsivity

In Report 3 eye-movement impairment was associated with poor habituation of SC responses as indicated by two measures of habituation (H-crit and H-inv) and the total number of SC responses (SCR tot) (Table 4). This relation was interpreted as the reflection by two independent indicators of a common underlying disturbance of

Table 4. Correlations between SPEM measures and SC measures (left hand),(SC habituation (H-crit and H-inv) and the total number of SC responses (SCRtot)) for the schizophrenic group in Study I.

SPEM measures	SC measures H-crit	H-inv	SCRtot	n
Session 1				
sin 1	.28	.28	.31	11
sin 2	.53+	.71**	.59*	10
tri 1	.06	.12	.09	11
tri 2	.19	.11	.08	11
Session 2				
sin 1	.71*	.74*	.62+	7
sin 2	.95*	.85+	.75	4
tri 1	.92**	.64+	.62+	6
tri 2	.78*	.47	.37	5

+ $p < .10$, * $p < .05$, ** $p < .01$.

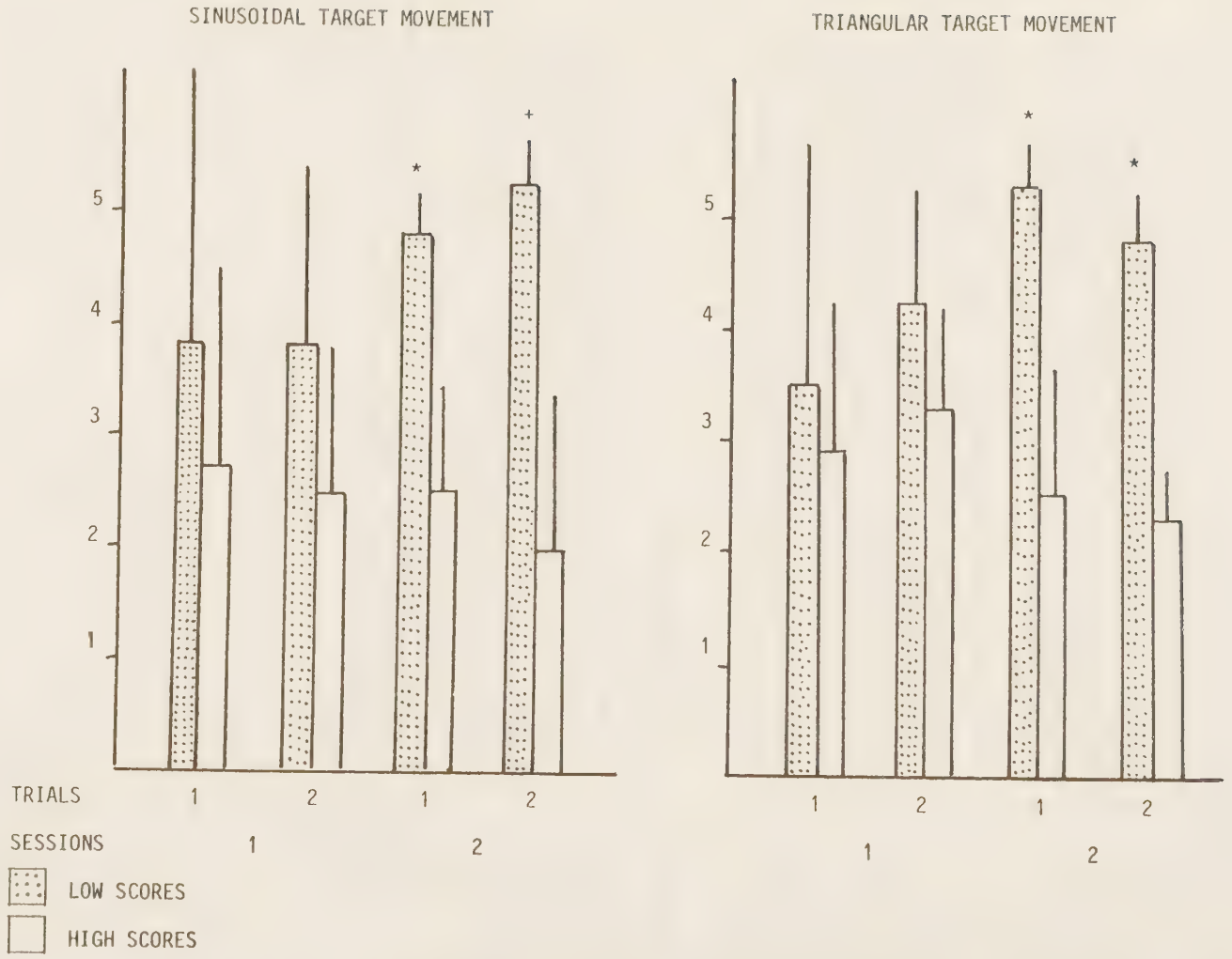

Fig. 3. Means and standard deviations of SPEM measures for the two types of target movements (sinusoidal and triangular) for schizophrenic patients with low (n = 3) and high (n = 8) scores on the Extended Psychosis Subscale of CPRS in Study I. (+ $p < .10$, * $p < .05$).

preattentive stimulus processing mechanisms. The findings were, however, not replicated in Study II with medicated patients.

SPEM and previous medication and hospitalization

Patients with previous antipsychotic medication and previous hospitalization had more impaired eye-movements (Report 3, Table 5, and Report 5, Table 3) which may be interpreted as effects of medication and hospitalization, per se. However, these factors may be confounded with other aspects of chronicity and type of disease, not covered by RDC subclassifications and CPRS ratings of severity of illness. Comparing the patient groups in the two studies (medicated vs unmedicated) it appears that patients with previous medication in both studies have similar degree of eye-tracking impairment regardless of medication status at the time of the SPEM recordings (Study I, unmedicated patients; Study II, medicated). However, medication-free patients who had never had antipsychotic medication (Report 3, Table 5) tended to have less eye-movement impairment than patients whose first antipsychotic medication period was at the time of the eye-movement registration (Report 5, Table 3). In the unmedicated group the dropout rate for the later trials was very high (54%) (Report 3) while in the medicated group all but two patients completed all trials (Report 5). It is not possible to conclude whether the high drop-out rate reflects inability to complete the task because of attentional deficits or lack of motivation. Spohn et al. (1977) reported a normalizing effect of phenothiazines on attention. Thus, it is conceivable that the schizophrenic patients in Study II were able to complete all trials, although poorly, as a result of clinical improvement due to medication. Systematic crossover studies are needed to investigate this hypothesis.

SPEM and brain morphological variables

As shown in Fig. 1 in Report 5 patients with the most impaired pursuit eye-movements tended to have the largest lateral ventricles. A positive relation between pursuit eye-movement impairment and increased lateral ventricles was hypothesized since observations in previous studies indicate that patients with increased lateral ventricles form a particular subgroup within schizophrenic patients which is characterized by predominantly negative symptoms (Johnstone, Crow, Frith, Stevens, Kreel & Husband, 1978), poor premorbid adjustment (Weinberger, Torrey, Neophytides & Wyatt, 1979), neuropsychological deficits (Donelly, Weinberger, Waldman & Wyatt, 1980; Golden, Moses, Zelarowski, Graber, Zatz, Horwath & Berger, 1980) and low levels of HVA and 5-HIAA (Nybäck, Berggren, Hindmarsch, Sedvall & Wiesel, 1983). However, the size of the lateral ventricles for all patients was well within the normal range (0.25 ± 0.06). Patients with occipital asymmetry tended to have more impaired eye-movements ($p < .10$).

SPEM and biochemical variables

In Report 3 eye-movement impairment was studied in relation to levels of monoamine metabolites of dopamine (HVA), serotonin (5-HIAA) and noradrenaline (MHPG) in the CSF. A relation between eye-movement impairment and low levels of HVA and 5-HIAA was expected on the basis

of preliminary findings in a larger group of psychotic patients; no such correlations were obtained in the present group of RDC diagnosed schizophrenic patients.

Computerized Neuropsychological Tests in Schizophrenic Patients

Three computerized neuropsychological tasks were designed for the present work (Report 4). Patients with previous antipsychotic medication and with previous psychiatric hospitalization (partly overlapping groups) showed significantly worse performance in Trail Making and lower number of Necker cube perceived alternations. Thus, subjects who had experienced more than one psychotic episode before the present one, and had been treated for it, displayed more evidence of neuropsychological deviance.

The results for the schizophrenic patients were compared with available data for a group of 84 healthy male subjects. In Finger

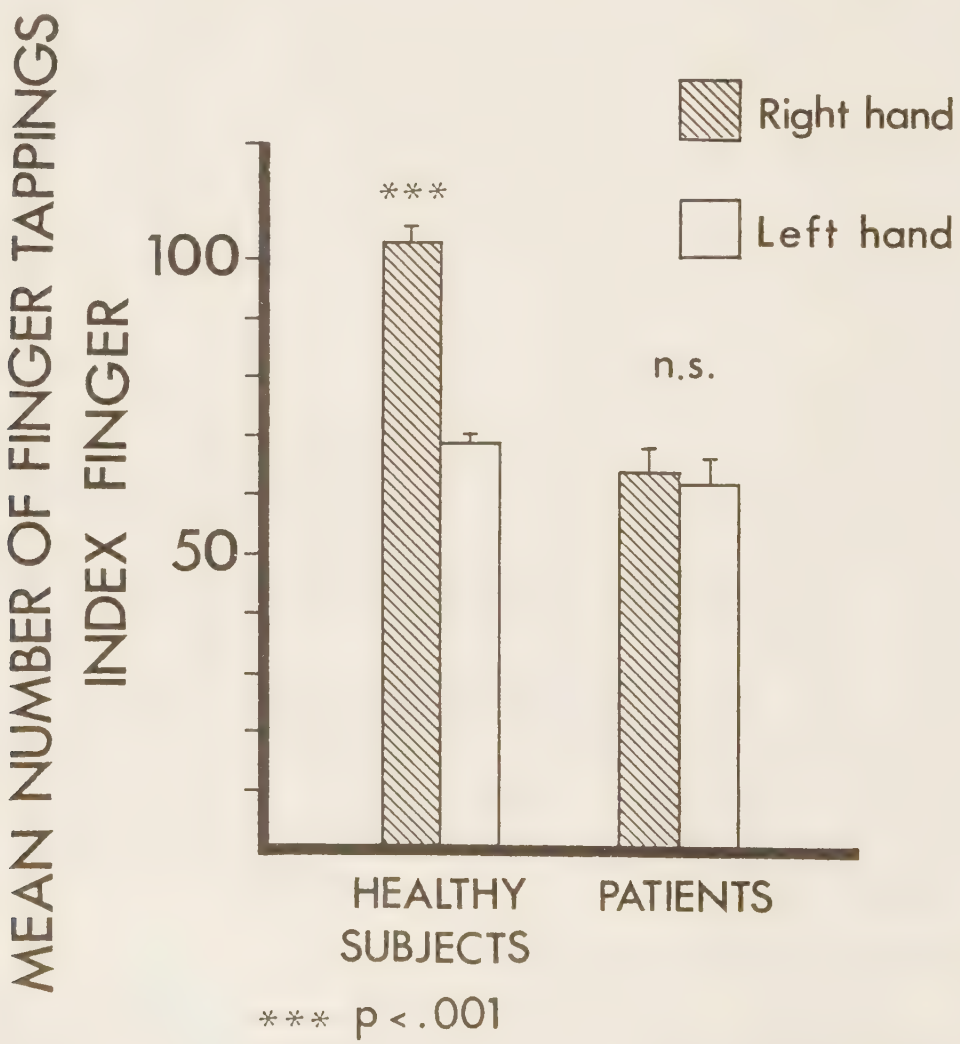

Fig. 4a. Mean number of finger tappings (index finger) for left and right hands for schizophrenic patients (n = 18) and healthy male subjects (n = 84) in Study II.

Tapping and Alternations, performance of schizophrenic patients did not differ from the comparison group for left hand (right hemisphere) measures, whereas there were highly significant differences for right hand (left hemisphere) measures, schizophrenic patients performing worse (Fig. 4a and 4b). It is unlikely that the results are due to differences in motivation and attention between the groups since these factors would have affected also left-hand performance in the schizophrenic group. Thus, the findings suggest a specific left-hemisphere impairment in schizophrenics as indicated by inferior right-hand performance in finger tapping. The cortical region involved in simple motor tasks such as finger tapping is situated in the premotor frontal association area (Kandel & Schwartz, 1981).

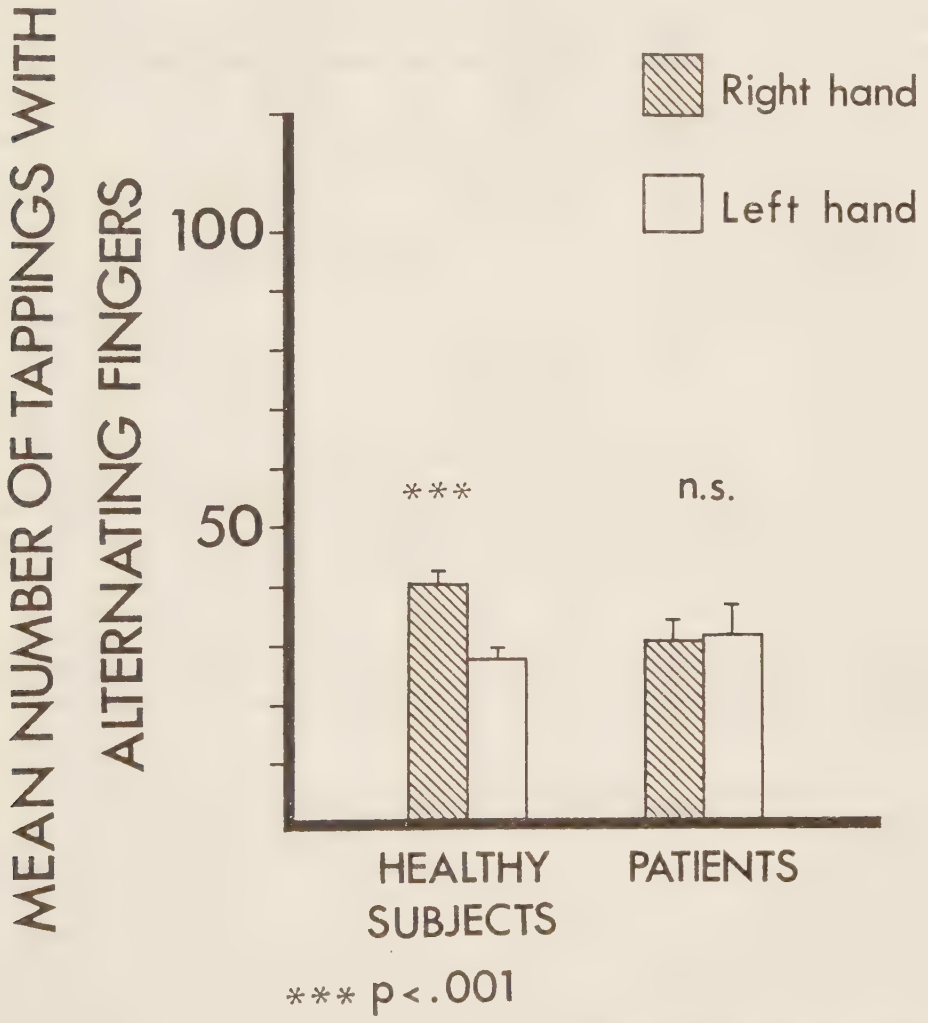

Fig. 4b. Mean number of finger tappings with alternating fingers for left and right hands for schizophrenic patients (n = 18) and healthy male subjects (n = 84) in Study II.

Schizophrenic patients were also inferior in Trail Making performance (Fig. 5). The difference was most pronounced for Form B measures, which involve more of left hemisphere components as compared to Form A. Form A involves components of visuo-motor coordination (assumedly right-hemisphere loaded) and visual search (assumedly fron-

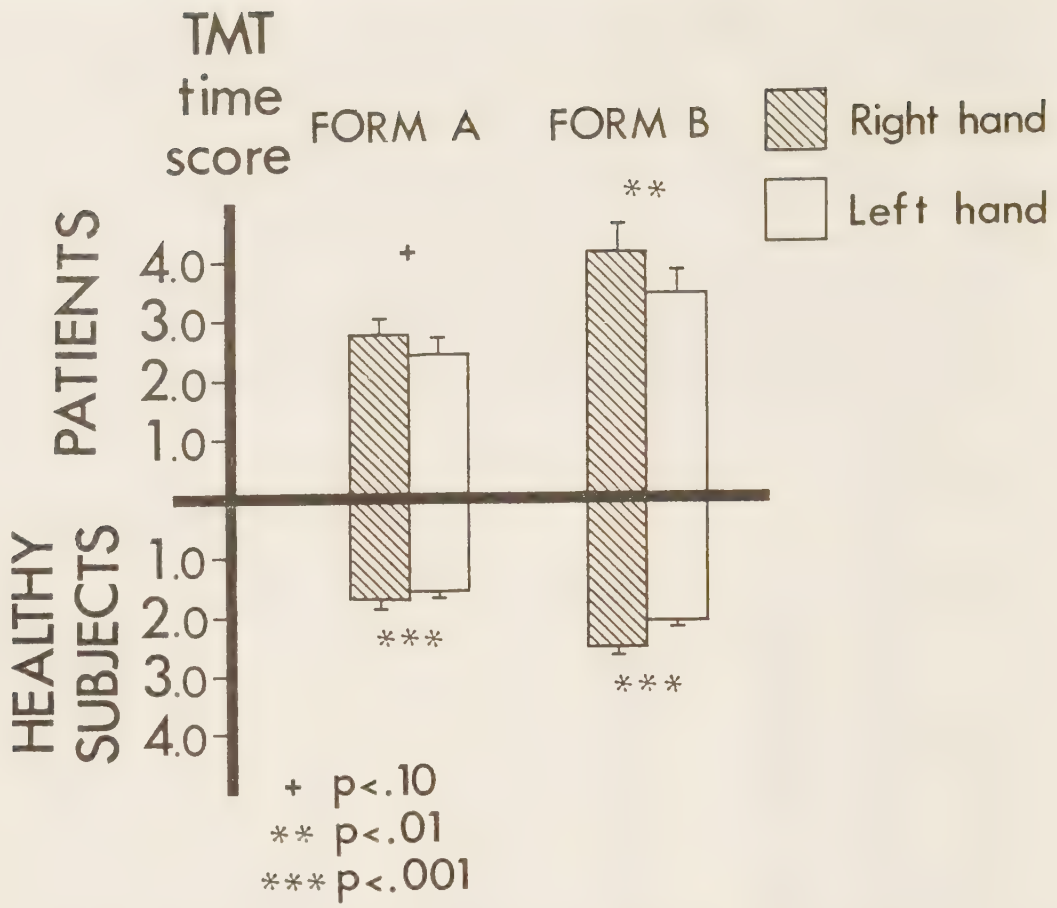

Fig. 5. Mean time scores in the Trail Making Test (Form A and B) for both hands for schizophrenic patients (n = 18) and healthy male subjects (n = 84) in Study II.

tal eye field function). Form B in addition also involves components of serial performance (assumedly frontal lobe and left hemisphere loaded).

Schizophrenic patients reported markedly fewer perceived alternations of the Necker cube. Latency (time to the first perceived alternation) did not differ between schizophrenics and healthy subjects, indicating that the difference in number of fluctuations did not depend on difficulties in understanding the task. Schizophrenic patients have displayed a lower number of perceived alternations also in two early studies (Hunt & Guilford, 1932; Nemor, 1953). Lower number of perceived alternations was found also for patients with unilateral frontal dysfunction (Cohen, 1959).

In conclusion, the pattern of results for the schizophrenic group and the comparisons between schizophrenic patients and healthy subjects in the three neuropsychological tasks consistently suggest a left hemisphere dysfunction/overactivation and a frontal lobe dysfunction in schizophrenic patients.

Neuropsychological measures and eye-movement impairment

Eye-movement measures were studied in relation to neuropsychological test performance in Report 5. Eye-movement impairment was related to slow finger tapping but not to finger alternations. Furthermore, eye-movement impairment was related to worse performance in the computerized version of the Trail Making test (Form A) and to fewer perceived alternations of the Necker cube (Table 5).

Table 5. Correlations between mean SPEM ratings for sinusoidal and triangular stimulus patterns and the three computerized neuropsychological tests, Finger Tapping (mean number of tappings) and Trail Making Test, TMT (mean performance time in sec) for both hands, and Necker cube (mean number of perceived alternations) for schizophrenic patients in Study II (n = 18).

Neuropsychological tests	Mean SPEM ratings	
	Sinusoidal patterns	Triangular patterns
Finger Tapping		
Index finger		
left	-.45+	-.59*
right	-.49*	-.69**
Index and middle fingers		
left	.03	.01
right	-.28	-.14
TMT		
Digits (A)		
left	.51	.43+
right	.56*	.51*
Digits and letters (B)		
left	.45+	.38
right	.37	.33
Necker cube (trial 1)	-.53*	-.50*

+ $p < .10$, * $p < .05$, ** $p < .01$.

Earlier findings indicate that some frontal cortical areas, particularly area 8, are involved in the regulation of smooth pursuit eye-movements (Bizzi, 1968; Levin, Holzman, Rothenberg & Lipton, 1981a). These areas have been assumed to be of importance for "visual search" (Teuber, 1964). Impulses from the "cortical frontal eye fields" to posterior parts of the brain are assumed by Teuber to serve as coordinators to achieve a smooth change of visual field during posture changes or whenever there is an alteration in the visual environment or stimuli. Performance on tasks similar to the Trail Making test Form A, and the rate of perceived alternations of reversible figures, such as the Necker cube, have been shown to change as a result of damage in frontal lobes (Cohen, 1959; Lezak, 1976). The correlations between SPEM impairment and deviance in the SC neuro-

psychological tasks support earlier indications of frontal lobe involvement in deviant pursuit eye-movements and contribute to a more comprehensive interpretation of the nature of pursuit eye-movement impairment.

DISCUSSION

Methodological Issues

Subjects

Selection procedures differed in the two studies. In Study I 37 patients with at least one psychotic symptom (hallucinations, thought disorders or delusions) were included initially. As described in the Method section the group was subjected to an extensive selection procedure resulting in the exclusion of 19 patients (51%). Only 17 satisfied RDC criteria for schizophrenia. Of these 17 patients two were excluded since they did not fulfill all criteria for inclusion in the study and two did not have satisfactory SC recordings. The high exclusion rate due to the application of rigid RDC criteria is not unique. A similar proportion of patients RDC-positive for schizophrenia among psychotic patients was reported by Nybäck, Wiesel, Berggren and Hindmarsch (1982).

One of the major difficulties in the evaluation and comparison of earlier findings in schizophrenia research has been the use of different diagnostic procedures, resulting in highly varying patient populations. The main purpose of the Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) was to create an instrument by which uniform and reliable classification and diagnosis of psychiatric patients could be obtained. There is one apparent disadvantage in using RDC with schizophrenic patients. Since the criteria require the presence of positive psychotic symptoms either present at the time of the clinical investigation or observed in a previous period, patients with schizophrenic features (for instance "negative symptoms") but no current positive psychotic symptoms, and no available information about previous psychotic symptoms will not be classified as schizophrenic according to the RDC criteria.

Both studies were conducted at the Psychiatric Clinic of the Karolinska Hospital. Psychotic patients consulting the emergency facility within the clinic, who consent to and are considered to be cooperative enough for treatment in an open ward setting, are referred to the psychosis research ward at the clinic. The clinic has no facilities for long-term hospital care. Patients, once relieved from the acute psychotic symptoms, are discharged and referred to community mental health centers and welfare facilities. When the improvement within a few months does not allow the patient to maintain an independent life in the community, or when the patient cannot cooperate within the open ward setting, the patient is referred to a mental hospital.

The probability is thus low that a patient with only negative symptoms consults the emergency ward and is admitted to the psychosis

research ward within the clinic. Among the 37 patients in Study I only three patients with schizophrenic features were excluded because of lack of positive symptoms. This restriction of range in symptomatology for patients participating in Study I is unfortunate since patients with relatively few positive symptoms appeared to have special characteristics in many of the measures studied in the present work. Patients participating in Study II were studied in a later phase of their illness, and most of them (90%) were on antipsychotic medication. Thus, these two factors are confounded in Study II, precluding direct statistical comparison between the patients participating in Study I and II.

Effects of medication

Generally, conclusions from studies on medicated patients must be made with caution since the medication might affect the measured parameters. There may be direct pharmacological effects on the measured functions, for instance anticholinergic and sympathetic ganglion blocking effects interfering with sweat gland activity (i.e. skin conductance measures). Furthermore there may be general medication effects either improving the clinical status of the patients, and thereby improving disturbed functions or motivation, or interfering with performance via sedation effects or specific CNS effects. In spite of the disadvantage of doing research on medicated patients, it was considered necessary to perform Study II on such patients. One important reason was that a study on unmedicated patients would require several years to accomplish. In some respects the results in Study I were unusual, and it was considered important to corroborate these findings on medicated patients, since most earlier studies have been made on patients under treatment. This was particularly important for the frequency of nonresponding. Further, it would present difficulties in generalization of the results since patients with acute psychotic symptoms who are able to carry out the attention-demanding neuropsychological tasks would probably represent a minor subgroup with special features within the schizophrenic population (cf. Spohn & Fitzpatrick, 1980).

Procedure and measures

Skin conductance and heart rate measures. Identical stimuli were used in Study I and II as to intensity (85 dB), duration (1 sec), frequency (1000 Hz), and rise time (0.25 msec). The tone intensity in both studies was rather high as compared to other studies. In Study I it was suggested that this intensity combined with the fast rise time of the tones contributed substantially to the lack of nonresponders in Study I among schizophrenic patients. However, the high frequency of nonresponders in Study II with identical stimuli considerably weakens this interpretation. There were some procedural differences between Study I and II. These differences would be expected to increase rather than decrease the incidence of SC responding and nonhabituating in Study II. A likely interpretation is that differences in nonresponding between the studies were due to differences between the two patient groups.

The present versions of the computerized *neuropsychological methods* are recently implemented, and all characteristics of the

tests have not yet been fully explored. Thus, caution is appropriate in interpreting the present results. The comparison of schizophrenic patients of both sexes with the presently available comparison group of randomly selected, young and age-homogenous males is not ideal. Bias effects of sex and age on the neuropsychological measures were statistically corrected for as far as possible. Since the order of subtests was not counterbalanced among subjects task effect was confounded with a possible order/training effect both for Tapping/Alternation and Trail Making. For Tapping/Alternation, which are relatively simple tasks, training effects are small within the present design. In contrast, there appears to be pronounced training effects for Trail Making. The reliability over tasks and trials of Trail Making measures both among schizophrenic patients and normal males were considerably higher than that reported for the paper-and-pencil version (King, 1967). The consistently high reliability coefficients argue against any marked inhomogeneity of training effects among schizophrenic patients. Thus, the result of group comparisons, both as concerns differences in performance and contrasts between subtests within groups, may be interpreted with some caution as effects of task and laterality rather than training effects. However, in comparing the absolute level of performance between right and left side, the confounding of side (right vs left) and order cannot be resolved within the present experimental design.

All *clinical ratings* were carried out independently from the results of the psychophysiological and neuropsychological measurements. The raters were trained and had had a long experience of the CPRS scale. Interrater reliability has been shown to be high for these raters (unpublished results).

General Discussion

In the present work two schizophrenic groups were selected on the basis of rigorous diagnostic criteria with high reliability to achieve a high homogeneity. Despite the diagnostic homogeneity of the groups (all patients satisfying the RDC criteria for schizophrenia), the results indicate a considerable heterogeneity with regard to psychophysiological and neuropsychological measures and to clinical symptoms. In spite of the small number of subjects in both groups, subgrouping according to clinical and psychophysiological data yielded meaningful results. A subgroup of patients who did not habituate to repeated identical stimuli, was characterized by relatively *few* psychotic symptoms. Patients with few psychotic symptoms also had more deviant pursuit eye-movements. Poor habituation was associated with deviant eye-tracking. Both types of impairments can be regarded as trait characteristics, since they are also present in healthy control groups (Reports 2 and 3), and they are not related to severity and phase of illness. They were interpreted to reflect deviance in preattentive stimulus processing.

One of the aims of the present study was to analyze the observed pattern of impairments within models of information processing. A model of particular interest for this purpose has been proposed by Öhman (1979) who tried to integrate Sokolov's model of habituation (1963) into a more general context of information processing.

This model comprises the following assumptions: (1) Stimuli are identified relatively completely (even including complex features such as semantic meaning) in an automatic and effortless manner with a close interaction with short-term memory storage. When there is a mismatch between the incoming stimulus and the representations available in the short-term memory storage, an orienting response (OR) is elicited. (2) The OR indicates a call to higher order central processing mechanisms to analyze the incoming information in relation to information stored in long-term memory. This central processing is of limited capacity which requires a serial processing strategy and the investment of mental effort. Serial processing strategies are currently assumed to be available mainly to the left hemisphere. Thus there is a link between the Sokolov-Öhman model and models of left-hemisphere functions, which makes it particularly interesting for research in schizophrenia, in view of the accumulating evidence of left hemisphere dysfunction/overactivation in schizophrenia.

According to the Sokolov-Öhman model poor SC habituation and irregular SC responding would indicate a continuous or often recurring mismatch between stimuli and their representations in the short-term memory, with a subsequent need for central effortful processing, leading to heightened arousal.

The findings in Study I (Reports 1, 2) of increased SC responsivity and high arousal are in agreement with this model, indicating some impairment of preattentive information processing mechanisms. Nonhabituators in Study II had higher arousal level than habituators and nonresponders. Earlier findings on acute, unmedicated schizophrenic patients also indicate higher arousal, as measured by SC level, SC spontaneous fluctuations and HR level (Bernstein, 1967; Zahn et al., 1968; Gruzelier et al., 1981; Tarrier et al., 1978).

The increased frequency of SC spontaneous fluctuations particularly in left-hand recordings in Study I suggests a larger increase in arousal in the left hemisphere, in line with current assumption of left-hemisphere overactivation in schizophrenia (Walker & McGuire, 1982; Gur, 1979).

Nonresponding can not be analyzed within the context of this model (Öhman, 1981).

According to the Sokolov-Öhman model a mismatch occurs when the current stimulus and its representation in the short- or long-term storage are not identical. The model does not explain *how* stimuli are identified by preattentive mechanisms. It postulates that this identification can reach a very complex level (such as semantic meaning). From an epistemological point of view no two stimuli (not even the simplest) are identical. The identification of stimuli involves a complex mental process where stimuli are constantly and automatically evaluated in a vast number of aspects for similarity. This implies a continuous evaluation of changes in the stream of input, and establishment of threshold levels for significant changes in relation to the mental representations.

Smooth pursuit eye-movements and SC habituation were interpreted as two independent indicators of preattentive stimulus processing

mechanisms in Study I. In Study II eye-movement impairment was further linked to some indicators of deficient frontal lobe functioning. According to Teuber (1964, p. 439) *one* of the functions of frontal lobes is to provide "continuous distinction between the relative motions of the environment which result from self-produced movement of the body and the true motions of objects in the surroundings". He continues: "Every 'voluntary' movement has two neural correlates: a stream of impulses to the effectors and a simultaneous "corollary discharge" to central receptor structures, presetting the latter for those predictable changes of input that will be the consequences of the particular motor output." The mechanism of the assumed "corollary discharge" is illustrated by involvement of the "frontal eye fields" in the oculomotor function, in visual search or tracking (Bizzi, 1968). Discharges from the "frontal eye fields" preset the posterior receptor fields for receiving the visual inputs subsequent to the oculomotor tracking movements, thus providing continuous feedback and prepare for imminent changes in the sensory input. This specific function may however be regarded as just one example of a general class of sensorimotor coordination phenomena which may depend on the integrity of frontal structures and portions of the basal ganglia.

The present data on eye-movement impairment and its relation to poor habituation and neuropsychological tasks reflecting frontal lobe functions are in line with a model of schizophrenia assuming disturbances in preattentive stimulus processing due to deficiencies in monitoring change of incoming stimuli. Thus, stimuli are more often perceived as "new", as indicated by the elicitation of the ORs, and therefore processed centrally. This overloads the central processing mechanisms as indicated by the high arousal level, and interferes with other ongoing cognitive processes.

Subjective experiences of perceptual aberrations well in line with these interpretations of the present results appear to be common in young schizophrenics. According to Chapman (1966), these may be seen long before the appearance of overt psychotic symptoms. One of the young patients interviewed by Chapman gives the following description:

Case 25. "I see things flat. Whenever there is a sudden change I see it flat. That's why I'm reluctant to go forward. It's as if there were a wall there and I would walk into it. There's no depth, but if I take time to look at things I can pick out the pieces like a jigsaw puzzle, then I know what the wall is made of. Moving is like a motion picture. If you move, the picture in front of you changes. The rate of change in the picture depends on the speed of walking. If you run you receive the signals at a faster rate. The picture I see is literally made up of hundreds of pieces. Until I see into things I don't know what distance they are away."

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ABBREVIATIONS

ANS	Autonomic Nervous System
CNS	Central Nervous System
CPRS	Comprehensive Psychopathological Rating Scale
CSF	cerebrospinal fluid
CT	computed tomography
DR	defense response
HR	heart rate
OR	orienting response
RDC	Research Diagnostic Criteria
SC	skin conductance
SCL	skin conductance level
SCR	skin conductance response
SF	spontaneous fluctuations
SPEM	smooth pursuit eye-movements
VDU	Video Display Unit
WAIS	Wechsler Adult Intelligence Scale

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